Introduction

When the heart fails the kidney retains sodium. Initially this is a beneficial counter-regulatory response to maintain the effective arterial volume, but the downside is an increased preload due to volume retention, which may perpetuate and even aggravate congestive heart failure (CHF). Diuretics counteract the sodium retention and are therefore indispensable in most patients with clinical heart failure. These drugs are clearly effective to reverse symptoms of congestion, but little information on their overall effect on prognosis is available. This point is important, since diuretics have several, potentially even life-threatening, side-effects.

A recent study has shed new light on a major problem regarding diuretic treatment in patients with CHF. Discussion of this study requires a review of some of the issues concerning current diuretic therapy to put the problem into perspective.

Volume overload—oedema

Patients with CHF may present with massive oedema. It is notoriously difficult to overcome the sodium retention in CHF. This is a compensatory response to the decrease in effective arterial volume and any further reduction in the effective arterial volume by diuretics may precipitate renal and/or circulatory failure. Furthermore, reducing preload by diuretics may worsen cardiac function, particularly in patients with right ventricular failure, although in many patients a reduction of preload and cardiac size brings the heart into a more favourable range of the Frank–Starling curve, thus increasing stroke volume [1].

Some patients with advanced heart failure may be resistant to even large doses of loop diuretics despite apparently normal renal function [2]. One important reason for the refractoriness to loop diuretics is the so-called rebound effect after single doses of loop diuretics, which is characterized by a disproportionately increased sodium avidity of the kidney after the diuretic action has worn off. This rebound effect may be overcome by a more frequent administration or the continuous infusion of loop diuretics. Should diuretic therapy with a single agent be insufficient, combination therapy with loop diuretics and distally active agents may be effective, even in patients with advanced renal failure [3,4]. However, this so-called sequential nephron blockade can induce severe electrolyte disturbances, in particular hypokalaemia and hypomagnesaemia. In this context potassium-sparing diuretics may be useful adjuncts to therapy. The aldosterone receptor blocking agent spironolactone may have a special role in this setting, since it provides blockade at a more distal nephron segment, as will be discussed below. It should be emphasized that a reduction of sodium intake will lower urinary potassium wasting and therefore reduce the risk of hypokalaemia. This is due to the fact that less sodium is presented to the nephron segment where potassium for sodium exchange takes place. A low-sodium diet will also help achieve a negative sodium balance, which is the ultimate goal of any rational oedema-reducing therapy.

Electrolyte disturbances

Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors reduces mortality in patients with symptomatic and even asymptomatic left ventricular dysfunction. Secondary hyperaldosteronism often persists, however, despite effective ACE inhibition. Consequently patients with CHF tend to develop hypokalaemia even when they are not on diuretics, particularly when the sodium intake is high. In patients with CHF severe hypokalaemia (and hypomagnesaemia) may develop, especially when high doses of diuretics are administered. Such hypokalaemia is not an innocent academic phenomenon, but a potentially life-threatening complication: patients with reduced left ventricular function have an increased incidence of severe cardiac dysrrhythmia and this tendency is aggravated by electrolyte disturbances.

When hypotensive patients are treated with high doses of diuretics the incidence of sudden cardiac death is increased [5,6]. At the 1998 meeting of the American Heart Association in Dallas a correlation was reported between diuretic dose and sudden death in patients with advanced heart failure; this finding was based on a retrospective analysis of the PRAISE trial [7]. In acute heart failure an association has also been found between diuretic use, clinical response and death [8]. Thus it appears that the benefit of diuretics with respect
to prognosis may at least partially be offset by fatal cardiac dysrhythmia.

In order to reduce the risk of arrhythmia, patients with CHF often receive oral potassium supplements, although this form of therapy is relatively ineffective for the prevention of potassium depletion. The cardiac risk of diuretic therapy can be reduced by prescribing low doses of diuretics and/or by the use of potassium-sparing agents [6]. In this context the aldosterone antagonist spironolactone has recently received much attention (RALES study; see below).

With appropriate caution potassium-sparing drugs may be added to the diuretic regimen even in patients who are simultaneously treated with ACE inhibitors. Such a combination requires meticulous monitoring of the serum concentration of potassium and creatinine, since a deterioration of renal function could rapidly result in life-threatening hyperkalaemia. It is useful to remember that reduction of sodium intake, apart from decreasing oedema formation and diuretic requirements, reduces urinary potassium loss. A low-sodium diet is therefore mandatory in patients with heart failure—even if hyponatraemia is present. A detailed discussion of the complex pathophysiology of hyponatraemia in (diuretic-treated) patients with heart failure is beyond the scope of this editorial. Suffice it to say that hyponatraemia mostly results from free water excess and not from sodium depletion. The treatment of choice is therefore restriction of free water intake. When this is difficult to achieve in patients with advanced heart failure, there may be a case for vasopressin antagonists—a new class of drugs on the horizon.

**Neurohumoral activation**

In addition to causing electrolyte disturbances, diuretics exert adverse cardiovascular effects by inducing a variety of neurohumoral alterations. Acute treatment with diuretics causes sympathetic activation [9] thus increasing the propensity to develop dysrhythmia. Chronic treatment with furosemide, however, decreases resting (but not exercise-induced) plasma noradrenaline concentration, while the renin—angiotensin—aldosterone system is activated [10]. Regimens recently proposed for the management of CHF include ACE inhibitors and—in selected patients—low-dose beta blockers. The latter should reduce neuroendocrine activation, but ACE inhibitors do not prevent the development of secondary hyperaldosteronism (see below).

**Persistent hyperaldosteronism—should all patients receive spironolactone? Evidence from the RALES study**

Hyperaldosteronism plays an important role in the pathophysiology of congestive heart failure, even in patients who receive therapeutic doses of ACE inhibitors which have become the backbone of modern CHF therapy [11]. The mechanism(s) underlying the so-called aldosterone escape are not known. Hyperaldosteronism favours the development of hypokalaemia and aggravates oedema formation. In addition to these clinically undesirable effects, aldosterone may also lead to structural changes of the heart, particularly cardiac hypertrophy and myocardial fibrosis [12]. Aldosterone-induced structural changes may contribute to the development of arrhythmia and adversely affect survival. Therefore it seems reasonable to block the cellular actions of aldosterone with spironolactone. This approach is fraught with the risk of hyperkalaemia, especially in patients who are on ACE inhibitors. The safety of the simultaneous treatment with spironolactone and ACE inhibitors has been a major concern. This issue was addressed in a multicentre trial in patients with CHF. The randomized aldactone evaluation study (RALES) enrolled 214 patients with congestive heart failure NYHA II-IV [13]. Spironolactone was added in a placebo-controlled fashion to the previous therapeutic regimen which included an ACE inhibitor and a loop diuretic. The doses of spironolactone ranged from 12.5 to 75 mg daily. The incidence of hyperkalaemia (K⁺ ≥ 5.5 mmol/l) was 5% in patients treated with 12.5 mg spironolactone per day and 13% in patients receiving 25 mg spironolactone per day; higher doses induced hyperkalaemia in up to 24% of patients. In the placebo group the incidence of hyperkalaemia was 5%. Hypokalaemia (K⁺ < 3.4 mmol/l) was observed in 0.5% of the treatment group and in 10% of the placebo group. The major conclusion of the RALES study was that in patients with CHF receiving ACE inhibitors, low doses of spironolactone (up to 25 mg/day) are safe and can effectively reduce the risk of hypokalaemia. Having established the safety/dosage of spironolactone the effect of spironolactone on mortality was evaluated in a multicentre placebo-controlled follow-up RALES trial on 1663 patients with severe CHF (NYHA III-IV). This study was terminated early because of a significantly reduced mortality in the spironolactone group; yet unpublished data presented at last year’s meeting of the American Heart Association in Dallas indicated a 27% decrease of mortality and a 36% reduction in CHF-related hospitalizations. However, it is currently not clear whether chronic aldosterone blockade affects cardiac structure in patients with CHF (as it does in animals), but reduction of vascular collagen turnover, improvement of heart rate variability, and reduction of the early morning increase in heart rate were noted [14]. The preliminary data from the RALES study suggest that these desirable effects translate into an improved prognosis. It is unclear whether there are significant differences between spironolactone and other potassium-sparing diuretics in this respect.

Acknowledgement. Prof. E. Ritz’s editorial input is gratefully acknowledged.
Introduction

The issue whether dietary protein restriction and pharmacological intervention retard the progression of chronic renal insufficiency (CRI) in man is extremely important. Its repercussions go beyond dialysis logistics and extend to issues such as patient suffering and the social and economic impact of regular replacement therapy (RRT). However, in the prospective of the patient, what he or she wants to know most is: ‘how long will I be free of dialysis if I follow therapeutic prescriptions?’ and ‘which is the most effective and least demanding therapy?’.

The effect of low protein diets

Over the last few years, there has been a considerable debate. There are nephrologists who claim that low protein diets have a limited effect on slowing CRI progression, basing their opinion on the results of large-scale intention-to-treat trials. On the other hand, there are those who admit that the effect is limited, but claim this is so only because compliance is less than optimal. This debate goes beyond the fate of individual CRI patients, since postponing the need for dialysis can save the community a large amount of money.

Statistical relevance

Although the conclusions of four prospective randomized and controlled trials [1–4] were inconsistent, the pooled results [5] showed that a low protein diet reduced the risk of renal failure or death in non-diabetic patients by 33% and this was statistically significant. Moreover, the pooled results of five studies of patients with insulin-dependent diabetes showed that a low protein diet significantly slowed the surrogate end points of urinary protein excretion or decline in renal function by 44% [5].

Clinical relevance

However, as indicated above, the key question is not so much whether protein restriction actually slows the progression of CRI, but rather whether the low protein intake is itself associated with an increased risk of death, and whether this deleterious effect has been underestimated in some studies.